REMARKS/ARGUMENTS

This is in response to the Office Action mailed October 17, 2008 for the above-captioned application. Reconsideration and further examination are respectfully requested.

This document accompanies a Request for Continued Examination. Applicants request and have paid for a two-month extension.

Claims 21-22 have been added to reflect specific embodiments of the invention. The claims are supported by the specification at paras. 50-55, and 67. In light of the Examiner's previous comments, Applicants have omitted previously submitted claim 23, which the Examiner refused to enter. No new matter has been added.

Enablement

Claims 1-3, 5, 7-9, 15, 17 and 19 stand rejected under 35 USC § 112, first paragraph, as lacking enablement. The Examiner asserts there is no enablement of a method wherein the therapeutic agent targets β4, or where the agent is an antibody that targets β4.

The Examiner states that the specification fails to show that agents that reduce the amount of active α6β4 and target and inhibit the signaling function of β4 inhibit angiogenesis. Applicants submit that the specification shows a relationship between inhibition of the signaling portion of β4 and inhibition of angiogenesis, and that one skilled in the art would understand that there are numerous ways to inhibit protein functions, including with antibodies.

The data given in the specification shows a relationship between inhibition of β4 and inhibition of angiogenesis. Experimental data showed that inhibition of the signaling/substrate portion of β4(the C-terminal end) leads to much lower complexity of vasculation in bFGF induced angiogenesis. Specification, para. 0057. This indicates that loss of β4 signaling impairs bFGF-induced angiogenesis to a significant extent. The data also showed that the substrate domain of β4 promotes endothelial cell migration and invasion in response to bFGF in human umbillical vein cells. Para. 0062 and 0063. In addition, the experimental data showed that β4 is expressed in significant levels in medium- and small-sized vessels of human papillary thyroid

carcinoma, breast adenocarcinoma, prostate carcinoma, and glioblastoma multiforme. Specification, para. 0054. Finally, the data showed that loss of activity of the substrate domain of β4 leads to reduced tumor growth in melanomas, lung carcinomas, lymphomas and fibrosarcomas, as well as corresponding reduction in microvessel density. Para. 0067.

In addition, the specification lists descriptions of effective antibodies and how to obtain them. It also lists numerous specific examples of antibodies for B4. *See* paras. 0029, 0039 anti-alpha-6 Mab CoH3 both human and mouse a6b1 and α6β4. Niessen et al., 211 (2) Exp Cell Res. 360-7 (Apr. 1994). The anti-beta-4 Mab ASC-3 blocks human beta-4 (Weaver et al., *beta4 integrin-dependent formation of polarized three-dimensional architecture confers resistance to apoptosis in normal and malignant mammary epithelium*, 2 Cancer Cell 205 (September 2002). Another known antibody is anti-beta-4 Mab 346-11A. (Zent et al. *"Involvement of laminin binding integrins and laminin-5 in branching morphogenesis of the ureteric bud during kidney development.*, 238 Dev Biol. 289 (Oct. 15 2001).

A person skilled in the art would also understand that phosphorylation of a protein may be inhibited by antibodies, especially considering the high level of skill in the art. For example, the anticancer drugs Trastuzumab and Pertuzumab, which are antibody based, are directed to the Ectodomain of ErbB2 to inhibit activation of ErbB2 and thereby phosphorylation of its cytoplasmic domain. *See, e.g.,* Rita Nahta, *The HER-2-Targeting Antibodies Trastuzumab and Pertuzumab SynergisticallyInhibit the Survival of Breast Cancer* Cells, 64 CANCER RESEARCH 2343 (April 1, 2004). Inhibition of phosphorylation of β4 would eliminate the signaling function in a manner similar to the removal of the signaling portion of β4.

The Examiner has offered no evidence that a person skilled in the art would not understand how to use an antibody to inhibit protein function, nor that said person would be unable to inhibit phosphorylation of a target protein with an antibody. A person skilled in the art would be able to combine the teachings of the disclosure with the knowledge in the prior art to construct an antibody that would inhibit the signaling function of β4, thereby inhibiting angiogenesis, without undue experimentation.

The Examiner has cited Hiran as teaching that α6β4 is not expressed during developmental angiogenesis. As used in Hiran, developmental refers to pre-natal, ie, in the womb. Hiran, at 3777 (whisker pads were taken from E19.5 embryos). This does not teach anything about post-natal angiogenesis. Hiran teaches that α6β4 is present post-natally and is a potential regulator of angiogenesis. *See* Hiran, at 3779. The fact that α6β4 is not present developmentally does not mean that a person skilled in the art would not know how to practice the invention. It merely possibly means that the invention may not work pre-natally.

The Examiner cites Sepp as teaching that inhibiting the function of β4 does not lead to inhibition of angiogenesis. Sepp merely discloses that use of two specific promoters of angiogenesis (bFGF and PMA) lead to a reduction of β4. The Examiner's argument ignores cause and effect, as well as the many reasons β4 may be reduced. The Examiner also ignores the statement that bFGF stimulation of bovine adrenal cortex endothelial cells induces an increase in β4 production. Sepp, at 270. In addition, as the Examiner has pointed out, the two functions of β4- adhesion and signaling- are quite separate. It is entirely plausible both that reduction of β4 adhesion would lead to angiogenesis and reduction of β4 signaling would lead to antiangiogenesis. Sepp does not provide any information about which function of β4 is reduced; it merely states that overall β4 is reduced. The experimental data provided in the specification shows that inhibition of signaling does have an antiangiogenic effect. The present invention concerns a reduction in the amount of signaling function of B4, not overall β4.

Because Applicants have shown that inhibition of the signaling function of β4 has an antiangiogenic effect, and a person skilled in the art would be able to inhibit this function with an antibody, the rejection for lack of enablement is in error.

Written Description

Claims 1-3, 5, 7-9, 15, 17 and 19 stand rejected under 35 USC § 112, first paragraph, as lacking written description.

The Examiner points to the terms "tissue expressing α6β4", "agent that targets β4" and "pathological angiogenesis in a tissue expressing α6β4 integrin" and states that Applicants have not provided enough examples to constitute a representative number of species nor provided a description of structural features that are common to species within each genus.

As to "tissue expressing α6β4", the Examiner points to Hiran to state that α6β4 is not expressed during developmental angiogenesis and states that no species in the specification are shown to express α6β4 during angiogenesis. While Hiran does state that α6β4 is not expressed during developmental angiogenesis, this only refers to pre-natal tissue. It does nothing to show that "tissue expressing α6β4" is not defined. In fact, it proves that a person skilled in the art is in possession of methods of determining whether a tissue is expressing α6β4 by proving that a negative result can be found. In addition to teaching that α6β4 is not expressed during developmental angiogenesis, Hiran teaches methods of detecting expression, such as immunostaining. Hiran, 3772-73. Therefore, a person skilled in the art would understand the meaning of "tissue expressing α6β4," as the Applicants use it in describing the invention, and it is fully supported by a written description.

In addition, the assertion that the specification teaches no species that express α6β4 is incorrect. The specification teaches numerous such species. For example, at paragraphs 0054 - 0055, human papillary thyroid carcinoma, breast adenocarcinoma, prostate carcinoma, glioblastoma multiforme, and melanoma are all shown to express α6β4 in medium and small vessels.

It is not necessary to describe all types of tissue that may express α6β4 during angiogenesis. Sufficient examples are given such that a person skilled in the art may determine whether a tissue is expressing α6β4 and appreciate Applicants' recognition of the general nature of the invention.

As to "agent that targets β4", as stated previously, numerous antibodies, oligonucleotides, and binding proteins have been discussed and disclosed by the specification. These provide some examples of potential agents. A person skilled in the art would be able to look at these agents, as

well as the knowledge that the C-terminal region controls signaling function, to determine characteristics of a broad range of agents that would target the known sequence of this region. Given the high level of skill in the art, practitioners would accept that an adequate description of α6β4 integrin would put an inventor in possession of antibodies, antisense oligonucleotides, and other agents that would target β4. Sufficient diverse examples with similar activity, such as antibodies and antisense oligonucleotides, have been provided to support this generic claim with written description.

As to "pathological angiogenesis in a tissue expressing α6β4 integrin", the specification provides methods of determining angiogenesis, such as with immunostaining. One target for this staining is PECAM-1, as described in para. 0054. Additionally, numerous tumor types that are associated with angiogenesis are described in para. 0067, such as melanoma cells, lung carcinoma cells, and lymphoma cells. Therefore, this term would be clear to one skilled in the art.

As stated previously, Sepp does not teach that inhibition of β4 does not lead to inhibition of angiogenesis. Sepp merely teaches that administration of angiogenic agents bFGF or PMA may reduce the amount of expressed β4. There is no indication that there is any causal relationship, nor is there a teaching of the function of β4 that is reduced. The experimental data given in the specification shows a relationship between inhibition of the signaling function of β4 and inhibition of angiogenesis.

Applicants submit that a person skilled in the art would understand the limits of the current claimed invention, and, utilizing this skill, would understand what potential agents and targets would be. It is not necessary to describe all potential targets, as sufficient structural limitations are given to describe these targets. Therefore, the rejection for lack of written description is in error.

Anticipation - Land

In addition, the Examiner has maintained his rejection under 35 USC § 102(b)/(e) for anticipation by Land (US Pat. Pub. 20030224993). Land teaches methods of inhibiting

proliferation of certain cancer cells by contacting the β4 integrin with a composition that inhibits ligand binding. The Examiner states that antibodies are disclosed at paras. 47-48.

To anticipate, the prior art must teach all the claim elements and the claimed arrangement. "Section 102 embodies the concept of novelty—if a device or process has been previously invented (and disclosed to the public), then it is not new, and therefore the claimed invention is "anticipated" by the prior invention. . . . Because the hallmark of anticipation is prior invention, the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" Net MoneyIn v. Verisign, No. 07-1565 (Fed. Cir. 2008). In an anticipation rejection, "it is incumbent upon the examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990).

Land does not teach all of the elements of the claimed invention. As the Examiner previously stated, the binding/adhesion function of β4 is quite separate from the signaling function, both spatially and temporally. Land merely teaches targeting of the binding portion, while teaching nothing about the signaling portion. This is the focus of the current invention, and Land teaches nothing about this.

In addition, Land teaches nothing about inhibiting angiogenesis. In the case of a method claim, a showing of anticipation requires that practicing the method described in the art would inherently (i.e. necessarily) achieve the undisclosed result which it the object of the claimed method, i.e. inhibiting angiogenesis. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990)(To establish anticipation under the theory of inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."). Land teaches inhibition of proliferation. The Examiner has given no evidence that targeting the β4 binding region would inherently result in inhibition of angiogenesis. As stated above, the two regions

have very different functions and locations. There is no way that targeting of one would inherently target the other.

Finally, particular antibodies are not disclosed in this reference. While the cited paragraphs generally state that antibodies may be used to inhibit function, no specific targets are given. There is no sequence or structure given for the antibodies, nor is a target given. In addition, even if a target were given, the antibody would not necessarily be functional to inhibit the signaling function of β4 as the only region discussed in the reference is the binding region of β4.

The Examiner states that the prior art agents would necessarily target the signaling function of β4. According to *Fitzgerald*, the PTO must have a reason to believe a functional limitation is an inherent characteristic of the prior art before a *prima facie* case is established and it may require the applicant to prove the prior art does not possess that characteristic. *In re Fitzgerald*, 205 USPQ 594, 596, 597 (Fed. Cir. 1980). In *Fitzgerald*, this only arose when the prior art was identical or nearly identical. Here, there is no indication given that the binding region of the reference and the signaling region of the claimed invention are similar. In fact, as the Examiner has pointed out, these regions are quite distinct. Therefore, the Examiner has failed to establish a *prima facie* case that the prior art agents would target both regions.

As Land does not disclose all of the elements of the current claimed invention expressly or inherently, it does not anticipate, and this rejection is in error.

Anticipation - Bennett

Finally, the Examiner has maintained his rejection under 35 USC § 102(e) for anticipation by Bennett (US Pat. Pub. 20060172957). This reference concerns antisense oligonucleotides for modulating the expression of integrin β4 binding protein, also known as eIF6 and eIF3A. *See* Bennett, para. 6

The β4 binding protein of Bennett is not the integrin β4 subunit of the instant claims.

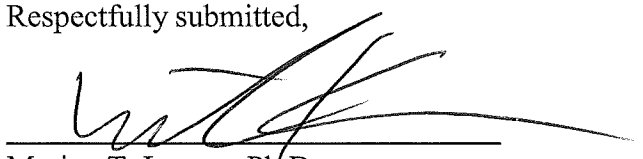
The binding protein of Bennett binds to the β4 subunit in vitro. *See* Wikipedia.org (EIF6). It is not the same as the β4 subunit. Bennett does not describe modulation of the integrin β4 subunit of the instant claims and therefore does not anticipate.

In addition, Bennett does not mention any targeting of signaling function of β4, nor does it mention angiogenesis. Also, there is no disclosure of the use of any antibodies as referred to in claims 5, 9, 17, 19, and 21-23. As stated above, in order to disclose, structure or sequence must be disclosed. The only mention of antibodies in the reference is for detection purposes, primarily Western Blots. There is no disclosure of antibodies for inhibitory use, particularly at a therapeutic level similar to the antisense used.

The Examiner cites paragraph 9 as teaching antibodies as a therapeutic agent. The text of paragraph 9 reads: "Currently, there are no known therapeutic agents which effectively inhibit the synthesis of integrin beta 4 binding protein and to date, strategies aimed at investigating integrin beta 4 binding protein function have involved the use of antibodies. Consequently, there remains a long felt need for agents capable of effectively inhibiting integrin beta 4 binding protein function." This clearly states the opposite of what the Examiner asserts. There are no therapeutic antibodies for β4, antibodies for β4 have only been used for investigation, and there is a need for antibody agents. Antibodies are clearly not disclosed as therapeutic agents.

As Bennett clearly does not disclose all of the elements of the current claimed invention expressly or inherently, it does not anticipate, and this rejection is in error.

Respectfully submitted,



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